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The goal of this training program is to significantly extend our existing, highly successful Interdisciplinary Doctoral Training Program in Tumor Biology with a new track which integrates genetics, molecular epidemiology, and prevention of breast cancer. This new track offers both MD/PhD and PhD training opportunities, and integrates new faculty from the Lombardi Cancer Center Programs in Cancer Prevention and Control, and Cancer Genetics. The program is enriched by new courses, as well as practical research experience. This programmatic initiative makes use of the existing organizational structure of the Interdisciplinary doctoral Training Program in Tumor Biology and incorporates a multi-disciplinary faculty who are devoted to research and education in breast cancer. We have successfully completed our fourth year of the program and recruited our fifth incoming class.

14. SUBJECT TERMS

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COMBINED M.D./Ph.D. TRAINING PROGRAM IN BREAST CANCER PREVENTION

INTRODUCTION

The goal of this program is to significantly extend our existing, highly successful Interdisciplinary Doctoral Training Program in Tumor Biology with a new track which integrates genetics, molecular epidemiology, and prevention of breast cancer. This new track offers both MD/PhD and PhD training opportunities, and integrates faculty from the Lombardi Cancer Center. The program is enriched by new courses covering cancer genetics, molecular epidemiology, and cancer prevention, as well as practical research experience. This new programmatic initiative makes use of the existing organizational structure of the Interdisciplinary Doctoral Training Program in Tumor Biology and incorporates a multi-disciplinary faculty who are devoted to research and education in breast cancer. We have recently had approved a request for an extension of this grant period from 4 years to 5 years, in order to optimize our recruitment of the best qualified candidates.

BODY

Training and Research Accomplishments

The accomplishments of this new program in its fourth year fall into two categories: the recruitment and progress of trainees, and the development of courses for the program. The Interdisciplinary Doctoral Training Program in Tumor Biology recruited, under this grant, 1 student in the current year and 2 students who will begin Summer 2003, Ogan Abaan, and Maria Silvina Frech.

The current year, in January 2003, we recruited Mrs. Youhoung Wang to the program. Mrs. Wang joins the Tumor Biology program with advanced standing as she has transferred from University of Illinois' Microbiology and Immunology PhD program and has a MS degree in Cellular and Molecular Biology from Sun Yat-sen University of Medical Sciences in China. Mrs. Wang has completed her first laboratory rotation with Dr. Dickson, and is now rotating in Dr. Hallgeir Rui's laboratory.

Ion Cotarla, M.D., appointed into the third year of the program in July 2001, has completed his comprehensive examination and is working on the regulation and function of Stat5 in normal and malignant mammary epithelial cells, in Dr. Priscilla Furth's laboratory. Riddhish Shah, M.D., appointed in July 2001, is continuing his thesis research project, TGF beta regulator region polymorphism and its functional significance, with Dr. Carolyn Hurley. Rita Kralik, MD, also appointed into the third year of the grant, has elected to take a MS degree in the program due to personal reasons.

Three trainees had been recruited for the second incoming class of the Breast Cancer Prevention Track of the Interdisciplinary Doctoral Training Program in Tumor Biology (see prior Annual Report): one MD/PhD candidate, Ms. Carolyn Lee, and two PhD candidates, Ms. Sonia de Assis and Mr. Elijah Herbert. Ms. de Assis is in her third year of the program. She has transferred from Dr. Peter Shield's laboratory and is now working with her thesis mentor, Dr. Hilakivi-Clarke. Her thesis project studies dietary factors during pregnancy and breast cancer. Ms. Lee is continuing her thesis research with Dr. Todd Waldman studying cancer genetics and breast cancer. Unfortunately, Mr. Elijah Herbert withdrew from the program after only a few months for very acute health reasons; we were able to use his slot in the program for recruitment of Ms. Carolyn Lee (above).

Two trainees had been recruited into the first incoming class, Ms. Christine Coticchia and Ms. Stacey Kessler (see prior Annual Report). Ms. Coticchia has received a DOD predoctoral fellowship, and is proceeding with thesis research with Dr. Robert Dickson, studying c-Myc mediated apoptosis in mammary carcinoma cells. Unfortunately, Ms. Kessler withdrew from the program for personal reasons, but she earned a Masters degree in Tumor Biology. However, the funds made available due to her departure were productively used to recruit a student with advanced standing into the third class.

In addition to the existing core course work of the Interdisciplinary Doctoral Training Program in Tumor Biology, new course components have been incorporated into the Breast Cancer Prevention track in Spring 2002. These include a course in Biostatistics, *Applied Biostatistics,* that has been refocused on statistical design and methodology for research rather than biostatistics theory, and a Cancer Genetics course, *Genetics, Health, and Society in the 21st Century*, which focuses on practical and ethical questions raised by genetic information and technology. Both courses have been very successful and continue to be offered. *Applied Biostatistics* has become a required course for Tumor Biology PhD and MS students. A new course in Genetics, *Human and Microbial Genetics*, had a successful first semester, and will be offered again next fall as an elective course.

All of these courses emphasize breast cancer, as most of the teaching faculty are extensively involved in breast cancer research. Interest in these courses has not been limited to students in the new Breast Cancer Prevention track: a number of additional students in the Interdisciplinary Doctoral Training Program in Tumor Biology and other biomedical graduate programs at Georgetown University have enrolled as well.

KEY ACCOMPLISHMENTS

- *Recruitment of New Trainees and Advancement of Existing Trainees:*

  Class #5

- The Tumor Biology department has recruited 2 new predoctoral students, Ogan Abaan and Maria Silvina Frech, to the Training Program in Breast Cancer Prevention. Mr. Abaan has received a MS degree in Biology from Middle East Technical University in Ankara, Turkey. Ms. Frech has received a MS degree in Food Technology from Universidad Catolica Argentina, and a MS in Biochemistry and Molecular Biology from Georgetown University. Both students will begin their first laboratory rotations in July, 2003 and will begin coursework in August 2003.

- **Class #4**
  Mrs. Youhong Wang was recruited to the program in January, 2003. She joins the program with Advanced Standing and will complete her coursework in 1 year. Mrs. Wang's project while rotating with Dr. Dickson was to study the effect of activated Preganancy-upregulated Non-ubiquitous CaM Kinase (PNCK) in breast cancer progression. Her current project with Dr. Rui is to study and develop new techniques involving competitive non-radioactive electrophoretic mobility shift assays for discovery of protein DNA binding sites.

Class #3
- Riddhish Shah, M.D. has successfully completed his comprehensive examination and is continuing in thesis research with Dr. Hurley.
- Ion Cotarla, M.D. has completed his comprehensive exam and is now in the thesis research portion of the program.

Class # 2
- Ms. Carolyn Lee has successfully completed coursework and her comprehensive examination and is continuing in Thesis Research.
- Ms. Sonia de Assis has completed her comprehensive examination and is continuing with Thesis Research.

Class # 1
- Ms. Christine Coticchia, from class #1 completed her comprehensive examination June 2001 and is currently progressing in Thesis Research.

REPORTABLE OUTCOMES

- *Student Publications:*

  - Ramljak D, **Coticchia CM**, Nishanian TG, Saji M, Ringel MD, Conzen SD, and Dickson RB. Epidermal Growth Factor Inhibition of c-Myc-mediated Apoptosis Through Akt and Erk Involves Bcl-xL Upregulation in Mammary Epithelial Cells. Experimental Cell Research, In Press, Corrected Proof, Available online 6 May 2003.

- Cavallio LR, Urban CA, Dai D, **De Assis S**, Tavares DC, Rone JD, Bleggi- Torres LF, Lima RS, Cavalli IJ, Issa J-PJ, and Haddad BR. Genetic and Epigenetic Alterations in Sentinel Lymph Nodes Metastatic Lesions Compared to Their Corresponding Primary Breast Tumors. Cancer Genet Cytogenet (In press) 2003.

- Waldman T, **Lee C**, Nishanian TG, and Kin JS. Human Somatic Cells Gene Targeting. In: Current Protocols in Molecular Biol. John Wiley & Sons. (In Press), 2003.

- Hruska KS, Tilli MT, Ren S, **Cotarla I**, Kwong T, Li M, Fondell JD, Hewitt JA, Koos RD, Furth PA, and Flaws JA. Conditional Over-Expression of Estrogen Receptor Alpha in a Transgenic Mouse Model. Transgenic Research 11: 361-372 2002.

- **de Assis S**, Ambrosone CB, Wustrack S, Krishnan S, Freudenheim JL, and Shields PG. Microsomal Epoxide Hydrolase Variants Are Not Associated with Risk of Breast Cancer. Cancer Epidemiology, Biomarkers, and Prevention 11(12): 1697-1698 2002.

- Hilakivi-Clarke L, Cho E, Cabanes A, **de Assis S**, Olivo S, Helferich W, Lippman ME, and Clarke R. Dietary Modulation of Pregnancy Estrogen Levels and Breast Cancer Risk Among Female Rat Offspring. Clin Cancer Res 8: 3601-3610. 2002.

- Hilakivi-Clarke LA, Cho E, **de Assis S,** Olivo S, Ealley E, Bouker KB, Welch JN, Khan G, Clarke R, and Cabanes A. Maternal and Prepubertal Diet, Mammary Development and Breast Cancer Risk.. J Nutr 2001, 131:154-157.

- Harris VK, Kagan BL, Ray R, **Coticchia CM**, Liaudet-Cooperman ED, Wellstein A, Riegel AT. Serum induction of the Fibroblast Growth Factor-binding Protein (FGF-BP) is Mediated Through ERK and p38 MAP Kinase Activation and C/EBP-regulated Transcription. Oncogene 2001 Mar 29;20(14):1730-8.

- *Student Abstracts/Presentations:*

  - **de Assis S**, Cabanes A, and Hilakivi-Clarke L. Alcohol Intake During Pregnancy Reverses the Pregnancy-induced Increase in p53 Expression in the Rat Mammary Gland. American Association for Cancer Research, Washington, DC 2003.

  - **Cotarla I**, and Furth PA. Critical Interactions Between Activated Stat5a and PI3K/Akt Signaling Pathways in Normal and Malignant Mammary Epithelial Cells. American Association of Cancer Research, Washington, DC 2003.

  - **Cotarla I**, Ren S, Li M, Zhang Y, Ghehan E, Singh B and Furth PA. Stat5 is Activated in Human Breast Cancers and Associates with the p85 Subunit of PI-3 Kinase. Georgetown University Department of Medicine Research Day,

Washington, DC; April 4, 2002. Graduate Student Organization Research Day; April 16-17, 2002. Meeting Abstract. Proc Soc Exp Biol Med, Washington D.C. Chapter Graduate Student Research Forum, Washington, D.C.; April 2002.

- **Cotarla I**, Ren S, Li M, Khan GA, Hilakivi-Clarke LA and Furth PA. Regulation and Function of Activated Stat5 in Normal and Malignant Mammary Epithelial Cells. Fourth Annual Lombardi Research Fair, Washington, DC; February 19, 2002; Georgetown University 16th Annual Student Research Day, Washington, DC; February 21, 2002.

- **de Assis, S**, Ambrosone, CB, Wustrack, S, Krishnan, S, Frudenheim, JL, Shields, PG. Microsomal Epoxide Hydrolase Polymorphisms and Tobacco Smoking in Relation to Risk of Breast Cancer. American Association for Cancer Research, San Francisco, CA, 2002.

- **de Assis S**, Ambrosone CB, Wustrack S, Krishnan S, Freudenheim JL, Shields PG. Microsomal Epoxide Hydrolase Polymorphisms and Tobacco Smoking in Relation to Risk of Breast Cancer. DOD ERA of Hope Meeting, Orlando, FL, 2002.

- **de Assis S,** and Shields PG. Microsomal Epoxide Hydrolase Polymorphisms and Tobacco Smoking in Relation to Risk of Breast Cancer. Fourth Annual Lombardi Research Fair. Georgetown University Medical Center, Washington, D.C. 2002.

- **Coticchia CM**, and Dickson RB. The Role of c-Myc Overexpression in Sensitization of Mammary Epithelial Cells to Apoptosis. DOD ERA of Hope Meeting, Orlando, FL, 2002.

- Ramljak D, **Coticchia CM**, Nishanian TG, and Dickson RB. AKT inhibits c-Myc-mediated Apoptosis in Mammary Epithelial Cells: A Mechanistic Investigation. DOD ERA of Hope Meeting, Orlando, FL, 2002.

- **Coticchia CM**, Wang J-K, Dickson R. Evaluation of Pathways Involved in C-Myc-induced Apoptosis of Mouse Mammary Carcinoma Cells. Fourth Annual Lombardi Research Fair. Georgetown University Medical Center, Washington, D.C. 2002.

- **Lee C,** Waldman T. Functional Analysis of PTEN in Human Cancer Cells by Human Somatic Cell Gene Targeting. Fourth Annual Lombardi Research Fair. Georgetown University Medical Center, Washington, D.C. 2002

- Selaru FM, Xu Y, Yin J, Shustova V, Zou T, Twigg C, Abraham JM, Mori Y, Sato F, **Cotarla I,** Greenwald BD and Meltzer SJ. Microarray and Bioinformatics Analyses Discriminate Among Biologic Subtypes of Esophageal Neoplasia. Meeting Abstract. Gastroenterology, 120 (5): 226, Suppl. 1, April 2001.

- *Awards:*

  - Christine Coticchia received a DOD Fellowship Award in 2001 - Fas/Fas L System on c-Myc Expressing Mammary Carcinoma Cells.

  - Ion Cotarla received a DOD Fellowship Award in 2003 - Nucleocytoplasmic Export of Stat5 in Normal and Malignant Mammary Epithelial Cells: Regulation and Implications in Breast Cancer.

CONCLUSIONS

The goal of this training program is to dramatically extend our existing, highly successful Interdisciplinary Doctoral Training Program in Tumor Biology with a new track which integrates genetics, molecular epidemiology, and prevention of breast cancer. Additionally, new course components have been incorporated into the Breast Cancer Prevention track that focus on cancer genetics, cancer prevention, and epidemiology and cancer risk.